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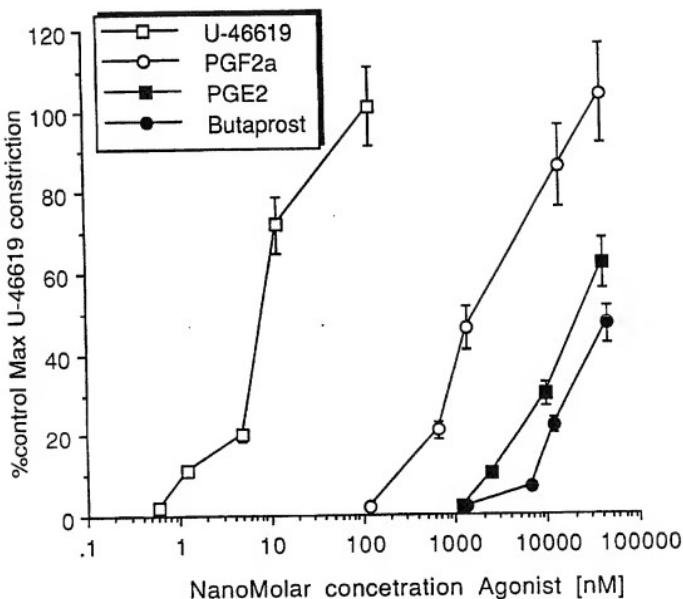
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(54) Butaprost compositions for preventing pre-term labour

(57) Compositions designed to achieve constant butaprost concentrations of less than 1μM at the myometrium surface inhibit uterine contractions while avoiding undesired side-effects and are useful in preventing preterm labour. The compositions are in the form of infusions, pessaries, gels or tablets and may further include anti-microbials, e.g. metronidazole or cefuroxime and/or inhibitors of bacterial prostaglandins, e.g. nabumetone, flusulide and SC 58125.

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COMPOUND FOR USE IN PRE-TERM LABOURBackground to the inventionField of the invention

5 This invention concerns the prevention of pre-term labour and in particular a compound for use in the management of pre-term labour.

Description of the Related Art

Pre-term delivery is a major cause of perinatal mortality and remains so, despite advances in obstetrics and neonatal care over the last decade. In any birth before 37 weeks
10 of gestation, over 80% of neonatal deaths are due to early delivery rather than foetal abnormality. Aggressive treatment using existing tocolytic therapy may cause distress to the mother and foetus and many clinicians question the relevance of such therapy since there are few obvious benefits to the foetus and the possibility of risk to the patient is increased. The value of tocolytic therapy in pre-term labour thus remains doubtful since
15 the incidence of pre-term delivery has not been reduced and prematurity is still the major contributing factor in neonatal mortality. The availability of modern technology allows the immature foetus to survive but the risk of permanent damage to the foetus and the cost of maintaining life are considerable. However, it is these advances in neonatal care, rather than improved tocolytic therapy, which have improved perinatal mortality rates in recent
20 years.

Existing tocolytic therapies as reported in the literature include the use of β-adrenoceptor mimetics such as ritodrine, salbutamol and terbutaline, magnesium sulphate and calcium channel antagonists. Other treatments under investigation include the use of oxytocin antagonists and prostaglandin synthesis inhibitors. However, these existing
25 treatments for pre-term labour lack efficacy and no novel treatments have emerged to alter the overall perinatal mortality and morbidity rate in the last decade. Clearly there is an urgent need to find a safe and effective way of halting pre-term labour and prolonging gestation.

Present prostanoid receptor classification states that each of the natural prostanoids
30 has its own receptor termed the P receptor where that particular prostanoid is at least ten

times more potent than any of the other prostanoids. Thus the prostaglandin E₂ (PGE₂) sensitive receptor is termed the EP-receptor and likewise PGF_{2 α} the FP-receptor; PGD₂ the DP-receptor; PGI₂, the IP-receptor and thromboxane A₂ (TXA₂), the TP receptor. The EP receptor, according to this classification based on selective agonists and antagonists in both 5 functional and binding studies, has been subdivided into at least 4 major subtypes, the EP₁, EP₂, EP₃ and EP₄. Smooth muscle activation of the EP₁ and EP₃ receptors usually results in stimulation of activity, whereas activation of EP₂ receptors usually results in relaxation and EP₄ activation results in dilation of certain vascular preparations.

Functional studies on human myometrium show the presence of EP₁, EP₂ and EP₃ 10 receptors on human myometrium. Selective prostaglandin agonists, antagonists and analogues as well as natural prostaglandins were used to characterise the receptors found on the human myometrium.

Senior et al. reports on the characterisation of receptors present on human myometrium in non-pregnant (Br J Pharmacol 1992 107, 215-221 and Br J Pharmacol 1991 15 102, 747-753) and term pregnant subjects (Br J Pharmacol 1993 108, 501-506). It was suggested that the potent inhibitory action of some synthetic prostaglandin analogues of these receptors could be useful in clinical hyperactivity states such as pre-term labour. Butaprost was mentioned as the most selective EP₂ receptor agonist used to date. Its use as a bronchodilator has been reported and it has been suggested for use in the treatment of 20 bronchial asthma (Nials et al., Cardiovascular Drug Reviews 11 1993, 165-179). It has also been shown that butaprost is dilator on human uterine artery in the micromolar concentration range (2-6) but was at least 100-fold weaker than PGE₂ suggesting that EP₂ receptors are not involved in this response (Baxter et al., 1995, Br J Pharmacol., 116 1692-1696).

25 The present inventor has surprisingly discovered that contrary to these reports, butaprost is actually not a suitable compound for use in the management of pre-term labour as the literature articles would predict. Firstly, *in vivo* the half life of butaprost is very low and unpredictably, butaprost has a constrictor effect on the human umbilical artery. Surprisingly since butaprost has a weak dilator effect on the human uterine artery, this was 30 not predictable. Thus this constrictor affect seems specific to the umbilical artery and is unusual which has the undesirable and dangerous side effect of causing foetal distress.

Summary of the invention

It has surprisingly been found that butaprost when locally applied in a consistent dosage can be useful in the management of pre-term labour without the associated dangerous or undesirable side effects outlined above. Accordingly, the current invention
5 is based on the observation that for butaprost to be a useful tool in the management of pre-term labour it must be at a concentration of less than 1 micromolar at the myometrium and present at a consistent level over a long period of time.

Thus according to a first aspect of the invention there is provided a pharmaceutical composition comprising butaprost for the treatment of pre-term labour wherein the
10 composition is adapted to ensure that the concentration of butaprost at the myometrium surface is substantially constant and at a concentration of less than 1 micromolar.

Description of the Preferred Embodiments

In the research directed towards the study of receptors on the human myometrium, many EP agonists have been employed but few show absolute selectivity for the individual
15 EP₁, EP₂ and EP₃ receptor types. Senior et al. (Br J Pharmacol 1993, 108, 501-506) reports that butaprost is the most selective EP₂ agonist used to date but, although inhibiting myometrial activity it was reported by Lawrence & Jones (Br J Pharmacol 1992, 105,
817-824) to have a constrictor effect on chick ileum and thus would not be indicative of any clinically useful role in pre-term labour management. This, coupled with the recent
20 observations about a contractile effect on the umbilical artery effectively rule out butaprost as a serious approach to the management of pre-term labour. The full range of prostanoid receptors implicated in this response are not known but it is thought that thromboxane receptors account for at least 50%.

The observations that the concentrations of butaprost actually required for
25 myometrial inhibition is less than the concentrations for toxicity and constrictor activity to become apparent lie at the heart of the invention. The problem is one of ensuring that the concentration of butaprost at the myometrium is correct to have advantageous and not disadvantageous effects.

The pharmaceutical composition of the present invention is adapted to achieve this aim. Thus, the concentration of butaprost at the myometrial surface is achieved over long periods of time by various methods. For example, a patient could be given a continuous infusion of butaprost. More preferable are controlled release formulation such as pessaries, 5 gels and tablets. These have an added advantage of being locally (intravaginally) applied.

Most preferred are controlled release compositions comprising butaprost and a polymeric composition according to GB 2047094B, the contents of which are incorporated herein by reference.

Suitable dosages will depend on individual cases but generally will be in the range 10 10nM min⁻¹. This dosage will maintain the necessary concentration of butaprost at the myometrial surface and can be maintained as long as necessary from hours to weeks depending upon the needs of the patient.. Preferably, retrieval devices are included if the composition takes the form of a pessary.

It has often been difficult to diagnose and manage pre-term labour which has led to 15 inappropriate use of drugs. In some cases pre-term delivery is induced by pathogens present in the maternal reproductive tract. In such cases, appropriate antimicrobial therapy is provided. This is an area where treatment is promising in the management of pre-term labour. Conveniently then, the pharmaceutical composition of the present invention also includes an antimicrobial for the management of this infection. Currently used 20 antimicrobials which may be applied topically for this condition and are thus suitable for inclusion in a controlled release locally applied formulation such as a pessary, include metronidazole and concentrations in the range of 1mg Kg⁻¹ bodyweight hour⁻¹ are desirable. It would also be useful to administer butaprost intravaginally as described hereinabove together with systemically administered antimicrobials e.g. cefuroxime either 25 by infusion or orally.

Additionally, pre-term labour is often induced by bacterially induced prostaglandins. The enzyme prostaglandin G/H synthase-2 (PG HS-2) also named cyclo-oxygenase 2 is responsible for this synthesis and hence, the pharmaceutical composition of the invention together with or instead of the antibiotic also includes an 30 inhibitor of this enzyme. Inhibitors include nabumetone, flosulide and SC 58125 and a concentration range of 0.01-0.1mM is preferable.

It will be appreciated by a person skilled in the art that a person in pre-term labour can be supplied with any combination of the above described pharmaceutical compositions depending upon whether or not there is an infection of the maternal reproductive tract when the patient presents herself.

- 5 The invention will now be illustrated by way of Example with reference to Figure 1 which shows the effect of various prostanooids on the human umbilical artery *in vitro*.

Example 1

Inhibitory activity of butaprost on human myometrium

Method

- 10 Samples of gestational human myometrium (term pregnancy) from the lower segment were removed at elective Caesarean section (non-labouring) and set up in a superfusion apparatus (n = 8). Tissues were tested for sensitivity by administering PGE₂ (5nM) as a bolus dose and only those strips which responded with a biphasic or inhibitory response were used. The concentration of butaprost was administered in the superfusate 15 over a 15 min period and the number of tissues responding with complete inhibition of myogenic activity was recorded.

Results

- 20 Butaprost at a concentration of 0.1 micromolar administered over a 15 min period caused complete inhibition of myogenic activity. The mean recovery time for the myogenic activity after cessation of superfusion of butaprost (0.1 micromolar) was 22 % 5 mins. No stimulation of uterine activity was noted at any dose of butaprost investigated.

The EP₂ agonist, butaprost, is a potent inhibitor of human myometrial activity and is devoid of stimulant action.

The results are shown in Table 1 below.

TABLE 1

The % of samples of human myometrium from pregnant donors responding to the EP₂ agonist, butaprost, at various concentrations.

| | <u>Concentration of butaprost</u> | <u>No response</u> | <u>Complete inhibition</u> |
|----|-----------------------------------|--------------------|----------------------------|
| 5 | 1nM | 100 | 0 |
| | 10nM | 75 | 25 |
| | 0.1μM | 0 | 100 |
| | 1μM | 0 | 100 |
| 10 | 10μM | 0 | 100 |

Example 2

Umbilical Artery - effect of butaprost and other prostanoids

Method

The specimens of umbilical cord were set up in the laboratory within 120 mins of
5 delivery of the foetus. The artery from the central section of the cord was dissected free of connective tissue and immersed in Krebs solution containing indomethacin 2.79 micromolar gassed with 2.5% O₂ 8% CO₂ 89.5% N₂ at 37°C. Cumulative dose-response curves were obtained from agonists.

Results and Conclusions

- 10 Preliminary results using various prostanoid agonists are shown in Figure 1 (n = 4). The EC₅₀ values for other agonists used are shown in Table 2. The thromboxane mimetic, U46619, is a potent constrictor of human umbilical artery *in vitro*, suggesting the presence of TP receptors on this tissue. The constrictor effects of PGF_{2α} and PGE₂ occur at much higher concentrations, suggesting that these compounds may be acting through the
15 TP receptors rather than FP and EP receptors on this tissue. The constrictor effect of butaprost is surprising, since it is known to act selectively through EP₂ receptors which normally show relaxant effects. As can clearly be seen this constrictor effect of butaprost is only apparent at concentrations greater than 1μM.

TABLE 2

The EC₅₀ values for prostanoid agonists on human umbilical artery *in vitro*.

| Prostanoid | EC ₅₀ (μM) |
|-------------------|--------------------------|
| U46619 | 0.007 |
| PGF _{2α} | 5 |
| PGE ₂ | 20 |
| Butaprost | 60 |

CLAIMS

1. A pharmaceutical composition for the treatment of pre-term labour comprising butaprost wherein the composition is adapted to ensure that the concentration of butaprost at the myometrium surface is substantially constant and at a concentration of less than 1
5 micromolar.
2. A pharmaceutical composition according to claim 1 which is an infusion.
3. A pharmaceutical composition according to claim 1 adapted for controlled release.
4. A pharmaceutical composition according to claim 3 which is a pessary.
5. A pharmaceutical composition according to claim 4 wherein the pessary includes
10 a retrieval device.
6. A pharmaceutical composition according to any preceding claim which further includes an antimicrobial.
7. A pharmaceutical composition according to claim 6 wherein the antimicrobial is metronidazole.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
 GB 9518008.9

| Relevant Technical Fields | | Search Examiner MR S J PILLING |
|--|-------------|--|
| (i) UK CI (Ed.N) | A5B BKD | |
| (ii) Int CI (Ed.6) | A61K 31/557 | |
| Databases (see below) | | Date of completion of Search 27 NOVEMBER 1995 |
| (i) UK Patent Office collections of GB, EP, WO and US patent specifications. | | Documents considered relevant following a search in respect of Claims :- 1 TO 7 |
| (ii) ONLINE: MEDICINE, PHARM, WPI, JAPIO, CLAIMS | | |

Categories of documents

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| Category | Identity of document and relevant passages | Relevant to claim(s) |
|----------|---|----------------------|
| X | DE 3810081 A (BAYER AG) (05.10.89) see WPI Abstract Accession No 89-293672/41 | 1 |
| X | Br. J. Pharmacol. Vol 107, (Proc. Suppl. Oct) 1992, Yeadley H L et al, "A comparison of the inhibitory effects of prostanoid EP ₂ receptor agonists and β ₂ -adrenoceptor agonists." Abstract 90P | 1 |
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